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Chapter 11

Sex Hormones and Multiple Sclerosis

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Abstract

Experimental and clinical data about the influence of sex hormones on the course of multiple sclerosis (MS) grow rapidly during the past two decades. Estrogens, progesterone, and androgens have been shown to ameliorate experimental autoimmune encephalomyelitis (EAE) in animals, and pregnancy in women is associated with a dramatic reduction in disease activity. Immunomodulatory and neuroprotective properties of sex hormones are the most probable underlying mechanisms, creating a background for testing similar hormonal treatments in humans. Several pilot studies in this field present promising results, but larger trials are necessary to identify the adverse events and to estimate precisely the place of sex steroids in multiple sclerosis therapeutic strategies.

The objective of this chapter is to summarize the recent advances in the research about the effects of sex steroids in EAE and MS and to create a ground for the development of more powerful treatments in the future.

Keywords: EAE, immune modulation, multiple sclerosis, neuroprotection, sex hormones

1. Introduction

Gender differences, observed in many aspects of autoimmune diseases, also concern multiple sclerosis (MS) to a high degree. Experimental and clinical data have suggested a role of sex hormones in the pathogenesis of MS and disclose additional therapeutic possibilities.

Initially, empirical observations, such as female prevalence in susceptibility to MS, differences in the clinical presentation between men and women, and the effect of pregnancy on the course of the disease drew attention on the effects of sex hormones in the development of the

pathological process in MS. Female gender is now regarded as an independent risk factor for the development of the disease, with female:male ratio 3:1, and even higher (3.2:1) in subjects with MS onset before age 20 [1, 2]. Despite this incidence, women do not have poorer prognosis than men, suggesting a biological mechanism underlying these divergences. Pregnancy, the most potent disease-modifying factor in MS, is a physiological condition characterized with significant hormonal and immunological changes, which raises the idea that sex hormones are implicated in some aspects of the autoimmune process. Many of these observations have been confirmed and elaborated in experimental autoimmune encephalomyelitis (EAE).

The purpose of this chapter is to provide an updated, summarized overview of currently published scientific information about the role of sex hormones in the pathogenesis and clinical course of multiple sclerosis and to outline the perspectives to use this knowledge for control of the disease activity.

An advanced search was conducted, based on the following key words in different combinations: "multiple sclerosis", "experimental autoimmune encephalomyelitis", "sex hormones", "pregnancy", "cytokines", "estriol", "estradiol", "progesterone", "testosterone", disability", and "MRI". The relevant scientific works (original articles, book chapters, and systematic reviews) published in English, in electronic database (PubMed, MEDLINE, and Medscape) have been retrieved and summarized. The search period was unrestricted. The following inclusion criteria have been determined: (1) subjects, suffering from multiple sclerosis; (2) studies on EAE; (3) assessment of sex hormones and cytokines; (4) brain imaging findings in relation to hormonal concentrations. Case report articles were excluded. A relationship between the concentrations of sex hormones, cytokines, physical disability, and the course of the disease has been searched.

2. Sex hormones and the immune system

Many differences have been identified between men and women with respect to the immune responses. In general, women show higher immunoglobulin levels, but lower activity of cell-mediated immune reactions than men [3]. These differences result in the effects of two major groups of biological factors: endocrine (sex hormones) and genetic (X-chromosome) [4]. Unique immunological peculiarities are observed in women during pregnancy.

Sex hormones affect the immune system in various ways. Immune cells, such as T and B lymphocytes, monocytes, macrophages, natural killer (NK) cells, dendritic cells (DC), express receptors for sex hormones although the lymphoid cells are not their main target. Estrogen effects are mediated through two isoforms of estrogen receptors (ER)—ERα and ERβ. Two isoforms have been identified for the progesterone receptor (PR) as well—PRA and PRB, while androgen receptor has no variants and binds both testosterone and 5α- dihydrotestosterone [5–8].

The regulation of T helper 1 (Th1)-type cytokine production by estrogens, appears to be dose dependent. Some authors report increased production of IFN-γ and IL-2 by low, "physiolog-

ical" doses of estrogens, while others find them unchanged [9, 10]. Biphasic secretion of TNF-α has also been described, with stimulation by low doses and inhibition by high doses of estrogens [11]. Increased production of IL-4 by T lymphocytes has been registered after incubation with progesterone [12].

Studies on Th2 cytokine production (IL-4 and IL-10) do not reveal any effect of estrogens in normal conditions. No differences have been found between fertile and postmenopausal women in regard to IL-4 levels [13–15]. No differences in IL-10 production have been detected between women and men [10]. On the other hand, an enhancing effect of estrogen on IL-10 production has been found in T lymphocytes from patients with MS, suggesting potentially different regulatory pathways in autoimmune diseases [16, 17]. Consistent with these findings are the results from experiments, showing that estradiol at 10–100 nM inhibits lipopolysaccharide (LPS)-induced TNF-α production from human peripheral blood mononuclear cells (PBMCs) but is stimulatory in the absence of LPS. These data illustrate the importance of cellular context for the effect of estrogens on T cells—cytokine secretion [18].

In vitro, naïve T cells stimulated with CNS autoantigens in the presence of testosterone produce higher levels of IL-5 and IL-10, but decreased levels of IFN-γ [19]. Testosterone can also reduce the in vitro production of proinflammatory cytokines, such as TNF-α and IL-1β by human macrophages and monocytes [20, 21].

Concentrations of IL-1β producing monocytes have been found higher in men than in women [10]. The influence of estrogens on IL-1 production from monocytes and macrophages seems to be biphasic as well. Progressive inhibition of IL-1 transcription with increasing concentrations of estrogen and progesterone has been described in cultured peripheral monocytes [22]. The study conducted by Kramer et al. [23] demonstrated that 17-β-estradiol can mediate release of IL-1, IL-6, and TNF-α from activated monocytes and/or macrophages through modulation of CD16 expression, with low doses being stimulatory for CD16-expression and cytokine secretion, respectively. Clear evidence for dose-dependent effects of estrogens on cytokine secretion was revealed by Matalka [24]. At preovulatory concentrations, estradiol significantly enhanced IFN-γ, IL-12, and IL-10 secretion from stimulated whole blood cells. Concentrations, similar to those in pregnancy, have caused increased production of IL-10 and reduced IL-12, IFN-γ levels and IFN-γ/IL-10 ratio. In the same concentration, estradiol has been shown to increase IL-10 secretion and decrease expression of TNF-α mRNA in proteolipid protein (PLP)-activated peripheral blood mononuclear cells isolated from healthy subjects [17].

During pregnancy, ovarian secretion of female sex hormones gradually reaches the peak of physiological levels. At the same time, a shift from Th1 toward Th2-type immune responses is observed. Marzi et al. [25] have studied the antigen and mitogen-stimulated cytokine production by PBMC obtained from healthy women during pregnancy and postpartum, and has established decreased secretion of IL-2 and IFN-γ, and increased IL-4 and IL-10 expression in the last trimester of pregnancy [25]. Another study in healthy pregnant women has found reduced serum levels of IL-12 and TNF-α together with high estrogen and progesterone levels during pregnancy compared with puerperium [26]. Similar changes have been observed in pregnant women with MS [27].

Hormonal influences on the function of B lymphocytes have been assessed by the analysis of immunoglobulin levels. Higher immunoglobulin levels in women than in men are a part of the sex differences in immune responses [3, 4]. Kanda et al.'s [28] study has shown that estrogens increase IgG and IgM production in both males and females directly, and through a potentiating effect of IL-10, released from monocytes [28]. The effect of testosterone appears to be opposite, as it inhibits IgM and IgG production both directly and indirectly by reducing the production of IL-6 by monocytes [29].

Progesterone and estrogens have been shown to influence the activity of NK cells. Increased activity of these cells has been reported in postmenopausal women and men compared with fertile females in the luteal phase of the cycle [30]. Partially in line with these data are the results from experiments, investigating the direct effect of sex hormones on NK cells activity. High-dose estrogen elicits a suppressive effect, whereas progesterone, testosterone, and estrogen at physiological concentrations have no effect in vitro on established cell lines [31, 32].

There are evidence for estrogen impact on DC functions. Exposure of the immature cells to estrogen has increased their IL-6, IL-8, and MCP-1 production, but most importantly, has enhanced their capacity to stimulate T lymphocytes [33–35]. Another study has revealed the ability of estrogen to enhance DC proinflammatory cytokine production in animal models [36].

These findings demonstrate that the interactions between sex hormones and the immune system are extremely complex and variable during different physiological states. The dependence of hormonal effects on the concrete cellular context and local cytokine milieu suggests that some specifics might be present in pathological conditions and especially in autoimmune diseases.

3. Influence of gender and sex hormones on EAE

EAE, the most widely used animal model for MS, shares many common characteristics with the disease in humans regarding the gender and sex hormone impact on susceptibility and clinical presentations.

In the relapsing SJL murine model, EAE has the same sex bias as MS, with males being less susceptible to the disease than females [37–40]. The difference may result partially from the protective effect of testosterone in male mice. This hypothesis is supported by studies demonstrating that testosterone depletion via castration increases disease susceptibility [41]. In agreement with this are the results of Voskuhl et al. [42], showing greater severity of EAE when autoreactive T cells used for induction, were extracted from female experimental animals. Thus, the immunological processes leading to T-cell priming and induction of the immune response appear to be much stronger in female mice. Some strains of mice (C57BL/6, NOD, B10.Pl, and PL/J) do not show female prevalence in susceptibility [43, 44]. These data, together with the findings of Palaszynski et al. [45], showing that effects of androgen removal depend upon genetic factors, highlight the other key point—genetic background of gender differences in EAE and MS [45].

Very interesting results about differences between genders in the clinical course of EAE have been found by Smith et al. [40]. Both male and female SJL mice had chronic relapses, but the relapses in females were more distinct and severe than those in males, which had more gradual onset and milder clinical changes. Although male animals were relatively resistant to clinical disease in comparison to female animals, once a severe disease occurred, the older age group retained substantial clinical disease with more rapid accumulation of chronic neurological deficits [40]. In other strains, B10.Pl and PL/J, male mice have shown more severe disease than females [44]. Genetic differences, modifying the effect of hormonal status on the clinical course could account for the strain-specific disparities.

Pregnancy, the condition with the highest physiological levels of female sex hormones estriol and progesterone, makes experimental animals less susceptible to EAE. Numerous studies using rats, rabbits, guinea pigs, and SJL mice have confirmed that pregnancy reduces the incidence of the disease and/or delays the day of onset [46–50]. Data about clinical improvement of EAE during pregnancy are also highly consistent [42, 49–52]. Earlier studies could not find any histopathological differences between virgin and pregnant mice with EAE [49, 50], but a succeeding investigation found reduced CNS demyelination and cell infiltration during late pregnancy in animals with preinduced EAE [51]. Later on, an elegant experiment of Haghmorad et al. [52] has confirmed that pregnancy-induced alleviation of clinical manifestations is accompanied by reduced CNS demyelination and cell infiltration. Important information about the mechanisms underlying the amelioration of the disease activity is provided by examinations of the immunological changes related to pregnancy. Langer-Gould et al. [49] have found that serum obtained from mice in late pregnancy inhibits the proliferative response and IL-2 production of proteolipid protein p139-151-specific T cells [49]. In the study of McClain et al. [50] mice immunized during pregnancy produced less TNF-α and IL-17, and displayed an increased number of IL-10-secreting cells within the CD11b+, CD11c+, CD19+, and CD4+/CD25+ populations. Another study has confirmed suppressed production of IL-17 and TNF-α in cells from pregnant mice, compared to virgin controls with EAE [51]. Enhanced production of anti-inflammatory cytokines in splenocytes and increased percentage of Th2 and Treg cells in pregnant animals have been found by Haghmorad et al. [52]. Real-time PCR for transcription factors and related cytokines of Th1, Th2, Th17, and Treg cells in the CNS of the same animals have shown reduced expression levels of Th1 and Th17 transcription factors, and decreased Th1 and Th17 cytokines including IFN-γ, TNF-α, IL-17, and IL-23. The authors conclude that pregnancy and pregnancy levels of estrogen ameliorate the EAE by favoring Treg and Th2 differentiation in the CNS.

Since estrogens and progesterone concentrations increase progressively during pregnancy, the EAE model was used to determine whether elevation in levels of a certain hormone might be responsible for disease improvement. Two estrogens, estradiol and estriol, are increased during pregnancy. Although estradiol is present at much lower, fluctuating levels in nonpregnant fertile women and female mice, estriol is synthesized by the fetal placenta and is absent in nonpregnant states [53].

The effectiveness of both estrogens in different doses has been tested for suppressing EAE activity. Numerous studies have demonstrated reduction in the clinical severity of active and/

or adoptive EAE by estrogen treatment (17-β-estradiol or estriol) in different strains of mice (SJL, C57BL/6, B10.PL, and B10.RIII) [54–62]. Clinical amelioration has been achieved when estriol is used at doses producing serum levels that are physiologic during pregnancy. Estradiol has to be administered at doses, fivefold higher than in pregnancy in order to induce the same degree of disease protection, suggesting estriol is more potent to control EAE [54]. Now it is widely accepted that high doses of estrogens are protective. Data about the effects of low doses are divergent to some degree. Some authors have found that ovariectomy of female mice worsens EAE [58], whereas others have not observed any significant influence [42]. A study by Bebo et al. [56] has shown that both hormones in low doses reduce the ability of activated T-cells to induce EAE, but their administration after the onset of the disease does not decrease the severity of the clinical manifestations.

Histopathologically, the beneficial effect of estrogens is expressed by reduced leukocyte infiltration, demyelination, and neuronal damage in CNS, suggesting immunomodulatory and neuroprotective properties of sex steroids [57, 61–64]. Kim et al. [54] have found significantly increased production of IL-10 in cultured splenocytes obtained from estriol-treated animals [54]. Decreased number of TNF-α producing T lymphocytes in CNS and spleen suspension as a consequence of 17-β-estradiol administration has been demonstrated by Ito et al. [65]. Subramanian et al. [62] have observed a tendency toward reduced secretion of IFN-γ, TNF-α, and IL-6 from activated T lymphocytes along with decreased incidence and severity of EAE under ethinyl-estradiol treatment. The latter has also suppressed the migration of encephalitogenic T cells into the CNS through downregulation of chemokines. In addition, estrogen treatment has been shown to induce certain regulatory T cells and to impair the ability of dendritic cells to present antigen [58, 59, 66, 67]. Mature dendritic cells have been shown to decrease expression of TNF-α, IFN-γ, and IL-12 mRNA with estradiol treatment, and T cells, cocultured with dendritic cells that have been pretreated with estradiol, showed a shift from Th1 to Th2 cytokine production [59]. Estriol exerts a similar effect on DC. Estriol-treated dendritic cells exhibit decreased IL-23, IL-6, IL-12 mRNA expression and an increased secretion of the immunoregulatory cytokines TGF-β and IL-10 [68]. B cells also appear to be involved in estradiol's protective effects in EAE. Removal of B cells from EAE mice has abrogated its protective effects [69]. B cells from estradiol treated mice have shown increase in IL-10 production [70]. Although both ERs are expressed in the immune system and the CNS, studies using ERα-deficient mouse strains have shown that clinical protection from EAE by estradiol and estriol depends on signaling through ERα [60, 61]. Anti-inflammatory effects of estrogens are also proven to be mediated by ERα. Treatment with ERα-selective ligand has induced favorable changes in autoantigen-specific cytokine production in the peripheral immune system (decreased TNF-α, IFN-γ, and IL-6, with increased IL-5 production), and has reduced CNS white matter inflammation and demyelination in EAE [71]. These findings are confirmed by the studies of Tiwari-Woodruff et al. [64] and Gold et al. [72]. In addition to these peripheral effects, Garidou et al. [73] have found that ERα-mediated regulation of CNS microglial cells is important for amelioration of the disease.

Along with the impact on the immune responses, estrogens exert a direct neuroprotective effect. Treatment with estrogen has decreased glutamate- and TNF-α-induced apoptosis and

preserved electrophysiologic function in neurons [74–76]. Estrogen treatment has protected oligodendrocytes from cytotoxicity and has accelerated oligodendrocyte process formation [67, 77–79]. Tiwari-Woodruff et al. [64] have shown that neuroprotective effects of estrogens are mediated predominantly through the ERβ pathway. ERβ ligand treatment has promoted recovery during the chronic phase of EAE, reduced demyelination, preserved axon numbers in white matter, and decreased neuronal abnormalities in gray matter [80].

Progesterone is also considered capable of influencing pathological processes in EAE. Earlier studies have shown no effect or even augmentation of disease severity under progesterone treatment [55, 81]. These results contradict the well-documented amelioration of EAE by late pregnancy, when the highest physiological concentrations of female sex hormones are observed. Recent studies resolve these discrepancies. Pretreatment with progesterone has been shown to decrease disease severity and reduce axonal damage and demyelination [82, 83]. Yates et al. [84] have examined the treatment potential of the hormone, administered after the induction of EAE. Progesterone treated animals have shown reduced peak disease scores and cumulative disease indices, compared to the placebo group. The immunomodulatory effect of the hormone has been demonstrated by decreased secretion of pro-inflammatory cytokines IL-2 and IL-17, and increased production of anti-inflammatory IL-10, in addition to increased numbers of CD19+ cells and CD8+ cells. Inhibited Th1- and enhanced Th2-type immune responses by progesterone have been previously reported by Piccinni et al. [12], Drew and Chavis [85], Miyaura et al. [86], Hughes et al. [87], and De Leon-Nava et al. [88]. Neuroprotective properties of the hormone have also been evidenced in different experiments [89, 90]. Yu et al. [91] have shown that progesterone can promote successful remyelination in EAE. The results of the study using progesterone receptor agonist Nestorone for treatment of chronic EAE are promising. In addition to the decreased clinical manifestations and enhanced motor behavior in experimental animals, increased cell proliferation and doublecortin positive neuroblasts in the hippocampus have been found. Increased number of GABA-ergic interneurons and attenuated number of Iba1+ microglia/macrophages have also been observed. These data suggest possible activation of neurogenesis through progesterone signaling [92].

Kipp et al. [93] have studied the effect of estrogen and progesterone, given separately or in combination, on cuprizone-induced demyelination in C57B1/6 mice. Concomitant administration of cuprizone with either estrogen or progesterone reduced myelin loss when compared with the control animals. Simultaneous treatment with both hormones resulted in almost complete prevention of demyelination, suggesting mutual increase in their effects.

The clear detrimental effect of orchiectomy in EAE and the female prevalence in humans with MS has led to investigations of androgens' impact on the course of the disease. Foster et al. [94] have found decreased levels of this hormone in male mice during EAE relapse. Either testosterone or 5-α-dihydrotestosterone (which does not convert to estrogen) have been used for treatment of EAE. Both of them have shown protective effect in gonadally intact males of SJL and C57BL/6 strains [95]. Dihydrotestosterone has been effective in reducing the severity of chronic EAE in Dark Agouti rats (an experimental model showing a protracted relapsing EAE). Decreased gliosis and inflammation in the spinal cord has also been observed [96]. These results are in line with previous findings of Dalal et al. [97] who reported a less severe course

of EAE in dihydrotestosterone treated female SJL mice. MBP-specific T lymphocytes, derived from dihydrotestosterone-implanted females, have produced significantly higher levels of IL-10 than those from the placebo group. Bebo et al. [19] have demonstrated that testosterone reduces encephalitogenicity of myelin-reactive T cells: EAE induced by the adoptive transfer of androgen-treated T cell lines is less severe than disease induced with untreated T cell lines. In addition, decreased production of IFN-γ and increased secretion of IL-10 has been found in androgen-selected T cell lines compared to untreated cell lines. Taken together these data suggest different mechanisms of disease protection between endogenous physiological testosterone and exogenous supraphysiological androgen treatment. The study of Matejuk et al. [98] has demonstrated age-dependent differences in response to androgen therapy, with no protective effect of testosterone against EAE in middle-age males and almost complete resistance to the disease of young animals. These same authors found that testosterone inhibited proliferation of myelin oligodendrocyte glycoprotein 35–55-specific T cells and secretion of TNF-α and IFN-γ in young males, supporting the immunomodulatory properties of androgens.

There are evidence for direct neuroprotective effects of androgens. Testosterone has been shown to protect neuronal cell lines from oxidative stress and against β-amyloid toxicity induced cell death [99–101]. Experimental data suggest that neuroprotective properties of androgens are at least partially mediated through influence on expression of neurotrophic factors such as BDNF [102].

4. Clinical evidence for the effects of sex hormones on disease course

The onset of MS typically takes place during the childbearing period of life. It is well known that pregnancy has a strong influence on disease activity [103]. The effect of pregnancy in women with MS is in agreement with the experimental data, presented earlier in this chapter. A 70% decline in the relapse rate during the last trimester compared to prepregnancy period has been found in the largest study conducted by a French research group—the PRIMS study (pregnancy in multiple sclerosis). A rebound effect has been observed after delivery, with significantly increased frequency of relapses. However, the overall one-year effect (pregnancy + puerperium) on the relapse rate was neutral (the increase during the first three months of puerperium was balanced by the reduction during pregnancy) [104]. A number of earlier prospective studies with a smaller sample size have reported similar results [105–107]. A meta-analysis of 22 reports on pregnancy in MS has confirmed the overall effect of pregnancy and puerperium on disease activity [108].

The results of MRI studies are highly corresponding to the clinical observations. A small study has followed two patients with MS throughout pregnancy using MRI and showed similar reduction of MRI activity during the course of pregnancy and activation in the postpartum phase [109]. A consequent larger observation of Paavilainen et al. [110] has found a significant increase in the number of T2 lesions and DWI-positive lesions as well as in the total lesion load measured from FLAIR images after delivery, compared to the scans performed during

pregnancy. The majority of the active postpartum scans have been performed within 5 weeks of delivery, indicating that MS disease activation commonly takes place at a very early postpartum period. Interesting findings in the same study are the active lesions, observed in two patients at 35–37 gestational weeks, when blood estriol concentration begins to decline as a result of placental ageing. Consequently, the loss of high estriol concentrations might be one of the underlying mechanisms for an increase in MS activity after delivery.

The amelioration of MS in the last trimester of pregnancy is thought to be induced mainly by higher concentrations of estriol, estradiol, and progesterone, but human choriongonadotropin, human placental lactogen, prolactin, cortisol, 1,25-dihydroxyvitamine D3, α-fetoprotein, pregnancy-associated glycoprotein, blocking antibodies, and cytokines secreted by the feto-placental complex can also be involved. Pregnancy tends to suppress the immune system of the mother to prevent rejection of the semiallogeneic fetus [111]. "Physiological immune suppression" with change in the type of immune responses and cytokine production is regarded as one of the underlying mechanisms [112]. One of the important changes is the shift from Th1- to Th2-type of immune reactions [25, 27]. Langer-Gould et al. [113] have found a decline in IFN-γ producing CD4+ T cells during pregnancy but no increase postpartum. An increase in the level of Treg and Th2 populations and a decrease in Th1 and Th17 cells are typical for normal pregnancy [114–117]. The increase in Tregs has been shown to be mediated through the effects of estradiol on the immune system [118]. The total number of NK cells is reduced during pregnancy, both among patients with MS and among controls, before increasing again after delivery [119]. One study has correlated the postpartum relapses with an increased level of IL-8 in the first trimester [120]. Reduced HLA-G gene expression has been observed in the postpartum situation in all patients with MS but in none of the healthy controls. Decreased soluble HLA-G level has been associated with increased relapse status [121]. As the HLA-G CD4 T cells have suppressive properties and are characterized as a new regulatory T cell population, it can be hypothesized that reduced HLA-G expression contributes to the increased postpartum relapse frequency [103].

Menstrual cycle is another physiological state in women, associated with a specific fluctuation in serum sex hormones. Several studies have registered worsening of the neurological signs just before or during the menstrual bleeding in a majority of the patients, and in some women with MS the onset of all relapses was in the same phase of the menstrual cycle [122–125]. The precise mechanisms for these fluctuations are unclear but decrease in female sex hormones levels is highly probable.

Investigations on the serum concentrations of sex hormones in fertile women with MS have revealed relatively high incidence of disturbances. These findings are in accordance with disruption of estrus cycle homeostasis, observed in SJL/J mice with EAE [126]. One study found abnormally low serum concentrations of estradiol and/or progesterone in one or both phases (exacerbation or remission) of the disease in 60% of the patients and the levels of hormones significantly increased during clinical remission. Presence of hormonal abnormalities was associated with higher concentrations of TNF-α and IFN-γ, suggesting a suppressive effect of estradiol and progesterone on proinflammatory cytokine secretion. Less severe residual neurological deficit (in remission) was registered in patients with normal hormonal status

which could be attributed to additional neuroprotective effects of female sex hormones [127]. Another study has registered hormonal disturbances in 56% of women with MS and abnormal hormonal pattern correlated with the intensity of MRI pathology [128].

Little data are available about the impact of hormonal decline during menopause on the course of MS. Smith and Studd [129] have found increased disability in 54% of menopausal women with MS and Holmquist et al. [130] have reported worsening of MS symptoms related to menopause in 40% of the patients.

Onset of MS in men (age 30–40) usually occurs later in life than in women, coinciding with the age at which serum testosterone levels normally begin to decline [53]. Examination of serum testosterone concentrations has shown divergent results. Abnormally low levels have been found by Wei and Lightman [131] in 24% of male MS patients with primary or secondary progressive MS. Foster et al. [94] have observed the same disturbance in all four men (three with relapsing-remitting and one with secondary progressive MS) with sexual dysfunctions. On the contrary, male patients with relapsing-remitting MS, studied by de Andrés et al. [132] have presented elevated testosterone blood concentrations compared to the healthy controls and a tendency toward reduction during the relapse phase. The small sample size may account for these contradictory results, suggesting that larger studies are needed for more detailed examination of hormonal status and its relation to disease activity in MS. A recent longitudinal study, comprising 96 male patients with MS or clinically isolated syndrome, has found hypogonadal status (testosterone levels below the lower limit of normal) in 39% of the subjects. A negative age-adjusted correlation between total testosterone and EDSS has been revealed and higher baseline testosterone levels have been associated with less cognitive decline, measured by SDMT during longitudinal follow-up [133].

Gender differences are observed not only in susceptibility and clinical manifestations but also in brain damage characteristics. A study in a large cohort of MS patients has shown that men are prone to develop less inflammatory, but more destructive brain lesions than women [134]. Intracortical lesions are more frequent in men [135]. The relationship between sex hormone levels and tissue damage has been explored in MS. A MRI study of disease activity during different phases of the menstrual cycle has shown significant correlation between progesterone/17β-estradiol (PEL) ratio in the luteal phase and the number of gadolinium-enhanced CNS lesions [136, 137]. Another study has found a significantly higher number of Gd-enhanced lesions in women with abnormally low testosterone levels. In men, estradiol concentration has correlated with the volume of T1 lesions and the contrast-enhanced T2 lesions [138]. These data provide evidence that sex hormones modulate the development of brain tissue damages and repair in MS. Luchetti et al. [139] have extended the research in gender differences of steroid synthesis and signaling in the brains of MS patients. They have studied gene expression of these pathways and of inflammatory cytokines in MS lesions and normal-appearing white matter of male and female patients and controls. In MS lesions in males, local upregulation of aromatase (an enzyme involved in estrogen biosynthesis), ERβ, and TNFmRNA has been found; whereas in females, local upregulation of 3β-hydroxysteroid-dehydrogenase (a progesterone synthetic enzyme), and of progesterone receptor has been detected. Aromatase and ERαmRNA levels have positively correlated with that of TNF in primary cultures of

human microglia and astrocytes. Together these findings may represent contributing factors to gender differences in the brain damages and the course of MS, and suggest much more intricate interactions between CNS, endocrine and immune system.

5. Future perspectives

Promising results of testosterone, estrogens and progesterone in EAE have initiated pilot studies in humans, in which sex hormones are used separately or in combination with each other or with another immunomodulatory drug.

The first clinical study using sex hormones in women with MS has been performed with oral estriol 8 mg/day, given for 6 months to 10 patients (six with a relapsing-remitting course and four with a secondary progressive course). In the relapsing-remitting patients, the trial has been extended after a 6-month posttreatment period with a 4-month retreatment period, during which estriol has been given in combination with progesterone. Estriol treatment has decreased gadolinium enhancing lesion numbers and volumes on MRI, significantly increased production of IL-5 and IL-10 and decreased secretion of TNF-α. When estriol administration was stopped, MRI-lesions increased to pretreatment levels, but after treatment reinstitution, they significantly decreased again [140, 141].

Female sex hormones, given in addition to interferon-β therapy, have reduced the number of relapses and delayed progression of disability [142].

Larger, placebo controlled, clinical trials of estrogens in MS are ongoing. These include a multicenter placebo controlled trial of estriol in combination with glatiramer acetate (ClinicalTrials.gov: NCT00451204) and a trial, examining the potential of estradiol and progestin to prevent postpartum relapses—POPART'MUS trail (NCT00127075) [112, 143].

Ten male patients with relapsing-remitting MS have been treated with testosterone 100 mg/day via transdermal application for 12 months. Improvement of cognitive performance and slowing of brain atrophy, as measured by MRI, have been observed under testosterone treatment. Immunological changes consisted of decreased production of IL-2 and increased production of TGFβ1, BDNF, and PDGF-BB from PBMCs [144, 145].

The main expected adverse event about these high-dose hormonal treatments is the increased risk of malignancies. Data in the literature demonstrate that breast and uterine endometrial cancer are both mediated through ERα. Treatment with an ERβ ligand has shown neuroprotective effect in EAE and can be explored as a potential therapeutic strategy in multiple sclerosis [64]. On the other side, testosterone replacement is widely used in aging and hypogonadal men and there is no clear evidence that higher levels of circulating testosterone, within the physiological range, are linked to an increased risk of prostate cancer [80].

The variations in the susceptibility and in the clinical course of MS reflect the differences in immune responses between the genders. Now it is widely accepted that these differences are partially due to the impact of sex hormones. Estrogens, progesterone and androgens change

the cytokine secretion and interactions between immune cells and through this suppress the disease activity. Their direct neuroprotective properties enhance the amelioration of EAE and MS. Several pilot clinical trials using sex steroids as treatment agents in MS patients established positive results and need to be confirmed and expanded in larger cohorts.

In conclusion, a large amount of evidence about the influence of sex hormones on the pathological processes in MS has been accumulated. Although they are not a primary pathogenic factor, immunomodulatory and neuroprotective effects of sex steroids provide opportunities for development of new disease-modifying strategies.

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